PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

KELLER, Günter
Lederer & Keller
Prinzregentenstrasse 16
80538 München
ALLEMAGNE

LEDERER & KELLER
EINGANG / RECEIPT
07.01.2005
Erl.: . . . . . .

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 07.01.2005
Applicant's or agent's file reference 02021837.6	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/10701	25.09.2003	27.09.2002

Applicant
BIOMAY PRODUKTIONS- UND HANDELS-AKTIENGES... et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Tikka, K Tel. +49 89 2399-7830

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
02021837.6		

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/10701	25.09.2003	27.09.2002

International Patent Classification (IPC) or both national classification and IPC
C07K14/47

Applicant
BIOMAY PRODUKTIONS- UND HANDELS-AKTIENGES... et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.03.2004	07.01.2005

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Sprinks, M Telephone No. +49 89 2399-7706

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/10701

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-22 as originally filed

Sequence listings part of the description, Pages

1-6 as originally filed

Claims, Numbers

1-15 received on 17.09.2004 with letter of 17.09.2004

Drawings, Sheets

1/10-10/10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations

   see separate sheet

The following documents (D) are mentioned for the first time in this opinion/report; the numbering will be adhered to in the rest of the procedure:

D1: WO 99/34826 A (IMP COLLEGE INNOVATIONS LTD ;KAY ANTHONY B (GB); LARCHE MARK (GB)) 15 July 1999 (1999-07-15)

D2: NIEDERBERGER VERENA ET AL: "Calcium-dependent immunoglobulin E recognition of the apo- and calcium-bound form of a cross-reactive two EF-hand timothy grass pollen allergen, Phl p 7." FASEB JOURNAL, vol. 13, no. 8, May 1999 (1999-05), pages 843-856, XP002221491 ISSN: 0892-6638

General Observations

This Authority has carefully considered the Applicant's response to the issued Written Opinion. However, the comments and objections relating to lack of unity and inventive step expressed in said Written Opinion are essentially unchanged - see below. In summary, the technical effects of the truncated/mutated pollen allergens disclosed in the description are not considered surprising in the light of the teachings of D1 and D2, which teach that reduced reactivity with IgE antibodies after making such modifications was to be expected.

IV) Unity

1) SEQ ID Nos: 2 and 3 correspond to essentially different parts of Phl p 7, whilst SEQ ID Nos: 4-6 are full length and share one mutation in common.

   Consequently, at least three separate inventions are present in the claims (or more if the mutation shared between SEQ ID Nos: 4-6 does not provide a surprising technical effect - see section V below), these being:

   1) 2-EF hand allergen fragments corresponding to SEQ ID No: 2
   2) 2-EF hand allergen fragments corresponding to SEQ ID No: 3
   3) 2-EF hand allergen mutants with at least one mutation in common corresponding to SEQ ID No: 4 (e.g. SEQ ID Nos: 5 and 6)

2) In view of the fact that the approaches of truncating and mutating 2-EF hand allergens to reduce allergenicity were already known from D1 and D2, there is no technical relationship between the features of each of the above inventions that defines a contribution over the prior art.

3) However, in order to expedite the procedure and since all aspects of the application can be examined by this authority without significant extra effort, the Applicant has not been invited to pay additional examination fees at this time.

V) Novelty, inventive step and industrial applicability

Inventive step

1) The present application does not satisfy the criterion set forth in **Article 33 (3) PCT** because the subject-matter of **claims 1-15** does not involve an inventive step (**Rule 65.1 and 65.2 PCT**).

2) The present application is directed to pollen allergen fragments and/or mutants that have reduced IgE binding activity and are therefore less allergenic and more suitable for specific immunotherapy.

3) The general inventive concept of truncating allergens such as Phl p 7 in order to make them less allergenic is already disclosed in D1 (see page 9, lines 9-14 and page 66, lines 17-19).

Furthermore, D2 states:
"The fact that patients exhibited reduced IgE binding to certain Phl p 7 conformations may represent a basis for the generation of "hypoallergenic" allergen variants for specific immunotherapy. The latter concept has been used to generate recombinant fragments and mutants of the major birch pollen allergen Bet v 1 with reduced anaphylactic activity. Similar results may be obtained if the calcium binding sites of Phl p 7 are destroyed by site-directed mutagenesis" (emphasis added).

4) In view of D1 and D2, the general concept of truncating or mutating (particularly in the EF hand regions) the Phl p 7 allergen in order to make it less allergenic (particularly to reduce reactivity with IgE) was known. Consequently, the subject-matter of **claims 1-15** cannot be considered inventive in the light of D1 and D2 taken alone or in combination.

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amended Claims

1. A mutated polypeptide derived from the pollen allergen Phl p 7 selected from the group consisting of the sequences as shown in SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6, whereby said polypeptide has a reduced allergenic activity compared to wild type Phl p 7.

2. A polypeptide according to claim 1 which is capable of inducing an IgG response in a mammal.

3. A polypeptide according to claim 1 or 2 which induces a histamine release which is significantly reduced compared with wild type Phl p 7.

4. A polynucleotide encoding a polypeptide according to claim 1.

5. A vector or plasmid containing a polynucleotide according to claim 4.

6. A host cell transformed or transfected with a vector or a plasmid according to claim 5.

7. A method of preparing a polypeptide according to any one of claims 1 to 3 comprising culturing host cells according to claim 6 under conditions that said polypeptide is expressed and optionally recovering said polypeptide from said host cells.

8. A method of preparing a polypeptide according to claims 1 to 3 comprising chemically synthesizing said polypeptide.

9. The use of a polypeptide according to any one of claims 1 to 3 for the manufacture of a medicament for treating and/or preventing an allergic disorder.

10. The use according to claim 9 wherein the allergic disorder is allergy to a two-EF hand pollen allergen.

11. The use according to claim 10 wherein the allergic disorder is allergy to Phl p 7.

12. The use according to claim 10 wherein the allergic disorder is allergy to an allergen selected from the group consisting of Bet v 4, Bra r 1, Aln g 4, Bra n 1, Cyn d 7, Ole e 3, Syr v 3 and/or Phl p 7.

13. The use according to any one of claims 9 to 12 wherein the medicament is used for prophylactic vaccination.

14. A pharmaceutical composition comprising a polypeptide according to any one of claims 1 to 3 and a pharmaceutically acceptable carrier or diluent.

15. A pharmaceutical kit comprising a polypeptide according to claims 1 to 3 or a pharmaceutical composition according to claim 14.